Use Case II: Imaging Biomarkers and New Trends for Integrated Glioblastoma Management

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Abbreviations

ADC	Apparent diffusion coefficient
CHTH	Chemotherapy
DCE	Dynamic contrast-enhanced MRI
DSC	Dynamic susceptibility contrast
DSS	Decision support system
DWI	Diffusion-weighted imaging
EHR	Electronic health record
GB	Glioblastoma
GUI	Graphical user interface
Kep	Contrast extraction coefficient
Ktrans	Volume transfer coefficient
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRSI	Magnetic resonance spectroscopy imaging
NGS	Next-generation sequencing
PET	Positron emission tomography
PWI	Perfusion-weighted imaging
RCBV	Relative cerebral blood volume
RT	Radiotherapy
TMZ	Temozolomide
UX	User experience
WHO	World Health Organization

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16.1 Introduction

Glioblastoma (GB) implies a devastating prognosis with an average survival of 14–16 months using the current standard of care treatment [1]. GB is the most frequent malignant tumour originating from the brain parenchyma, and it is characterised by a marked intratumoural heterogeneity, proneness to infiltrate throughout the brain parenchyma, robust angiogenesis and necrosis as well as intense resistance to apoptosis and genomic instability [2].

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Up till now, treatment and follow-up of GB remains one of the most challenging tasks in clinical oncology. The critical points in GB management are related to neurosurgical and radiotherapy (RT) planning and early-response-to-therapy assessment. These points link with (1) maximum safe resection of the tumour; (2) local RT dose value, distribution and technique; (3) histopathology diagnosis in terms of GB molecular characterisation; and (4) duration of adjuvant chemotherapy (CHTH) and best treatment during follow-up.

Recently, important advances have been made in the multiscale (molecular-cellular-tissue-patient) study of GB through the identification of parallel and dynamic tumour markers by techniques such as next-generation sequencing (NGS), immunohistochemistry characterisation, radiogenomics, multi-parametric images and circulating biomarkers from liquid biopsies. These have led to the definition of different molecular subtypes of GB, with prognostic and predictive-of-response implications [3], although this molecular classification is not actually extended in the clinical practice.

Additionally, the number of imaging modalities and associated imaging biomarkers available for the assessment of patients is considerably high and probably will grow in the following years. These include perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI), magnetic resonance spectroscopy imaging (MRSI) and positron emission tomography (PET). Although the added value of medical imaging in GB diagnostic, prognostic and treatment assessment is unmistakable, it has been demonstrated that no single modality in itself is specific enough to reveal the early response to treatment of GB tumours due to their heterogeneity and rapid evolution [4].

In this setting, decision-making requires the joint analysis of complex data acquired throughout the treatment and follow-up process, including molecular biomarkers, imaging biomarkers and clinical data. Moreover, a comprehensive analysis of the data acquired from the patient requires taking into account the three main dimensions of GB data: multilevel dimension, from voxel to population-based subtypes; multiscale dimension, from molecular to tissue scale; and temporal dimension, from single to longitudinal studies.

To support the analysis of these complex data, in recent years, significant advances have been made in the development of automated medical image analysis tools for brain tumours. These tools are able to generate automated segmentations of the different GB-related tissues (i.e. oedema, enhancing tumour, necrosis), hypoxia maps and other useful nosological images. The last decade has also witnessed increased research efforts in the field of multiscale cancer modelling including the development of in silico (i.e. on the computer) oncology models able to simulate different therapy outcomes based on the individual patient information.

The purpose of this chapter is not only to introduce the role of imaging biomarkers in the GB management but also to identify and introduce the new trends that will contribute to the successful inclusion of these biomarkers in an integrative multiscale analysis. To do so, this chapter will focus on (1) the description of the standard clinical workflow based on accepted clinical guidelines, (2) the identification of the main open questions in GB management, (3) the role of imaging biomarkers in GB management and (4) the introduction of the new trends in GB management.

Moreover, this chapter introduces an approach of how these new trends could be integrated in the complex scenario of multidisciplinary teams enabling the access and analysis of multiscale and multilevel data. This approach is based on a modular clinical decision support system (DSS) architecture for GB management to easily include and actualise analytic modules. Moreover, an overview of the integration strategy based on user experience (UX) is described to ensure the acceptability of the DSS by the multidisciplinary clinical community.

Potential clinical benefits of incorporating this knowledge in the tumour board meetings include advances in surgery and RT planning, adjuvant treatment selection, assessment of response, early recurrence detection and selection of subse-

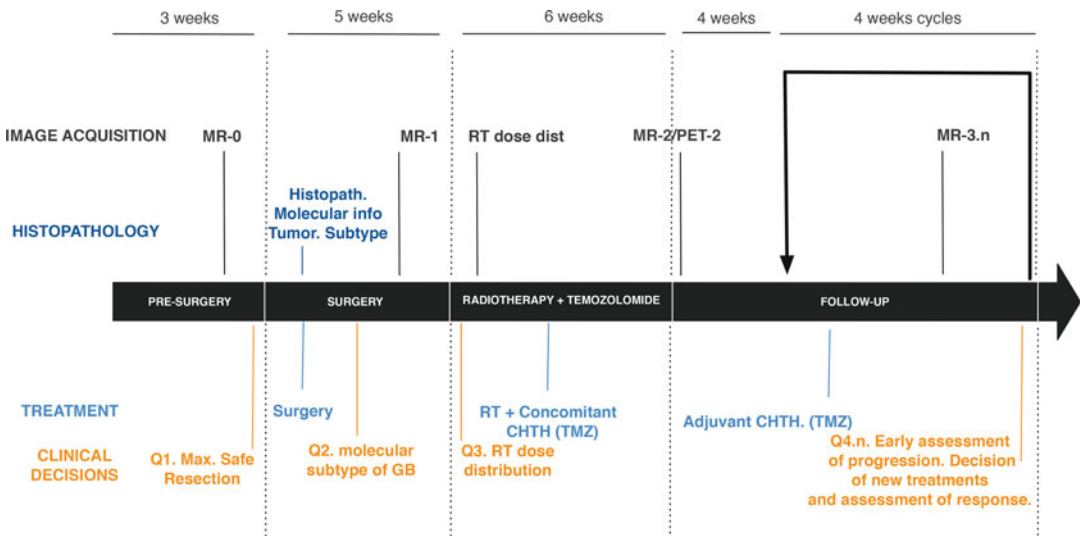

Fig. 16.1 Temporal diagram of the treatment and follow-up of GB patients including (1) the available clinical information at each stage, (2) the treatments (in *blue*) and (3) the main clinical decisions (in *orange*). RT dose dist. mean the information about the radiotherapy dose distribution. Q4.n and MR3.n mean the successive decisions and image acquisitions done during the follow-up, respectively

quent therapies. Moreover, this integrated approach will contribute to a better characterisation of GB subgroups, identification of new circulating biomarkers and identification of new targets for the treatment of patients with GB.

16.2 The Standard Clinical Workflow

Primary treatment after clinical or radiological evidences suggesting existence of GB consists on the maximum safe tumour resection based on the neurosurgical feasibility study. The extension of the tumour resection should be confirmed by postoperative magnetic resonance imaging (MRI) scan within 72 h after surgery, with and without contrast [5]. In case the resection is not recommended, a stereotactic or open biopsy or subtotal resection should be performed to establish the diagnosis. As soon as the pathology is available, the tumour expert panel or tumour board consultation is recommended.

After surgical intervention, the standard of care for newly diagnosed GB consists of adjuvant chemo-radiation therapy. In particular, surgery should be followed by RT and concurrent temozolomide (TMZ) CHTH and followed by six cycles of adjuvant TMZ. In the case of significant improvement on therapy, the inclusion of additional cycles of TMZ could be considered.

After the completion of RT, the follow-up of patients will consist on serial MRI scans. These MRI scans will be done in the second and sixth weeks (after RT), then every 2–4 months for 2–3 years and then less frequently [5]. The use of complementary imaging modalities such as MRSI, PWI or PET can be considered to facilitate the differentiation between pseudoprogression and radiation-induced necrosis.

In the case of local recurrence, a second resection is encouraged whenever it is possible. Following re-resection, or if the local recurrence is unresectable, poor prognosis patients should undergo best supportive care without further active treatment [5]. In case of diffuse or multiple recurring lesions, the options include surgery to reduce mass effect, the administration of systemic CHTH and best supportive care for poor prognosis patients.

The temporal diagram of the treatment and follow-up of GB patients is presented in Fig. 16.1.

16.3 Main Questions in Glioblastoma Management

Based on the above-mentioned standard clinical workflow, we could identify the following main steps in standard treatment for GB:

- Presurgery: to generate a first diagnosis based on medical imaging information
- Surgery: to remove the maximum safe area suspected to be affected by the tumour and to analyse the resected tissue to generate a more accurate diagnosis
- Concomitant RT with CHTH (based on TMZ): to irradiate the tumour tissue and to avoid the fast propagation of the tumour cells
- Follow-up including CHTH as adjuvant treatment to avoid the fast propagation of the tumour cells

In each of these four steps, important clinical decisions have to be addressed in order to select the most adequate treatment for each individual patient. Among them, the key decisions in GB diagnosis, therapy and follow-up are presented in the following subsections:

16.3.1 Presurgery Decision

What is the precise extension of the tumour that determines the maximum area that can be safely resected? Surgery of GB is by definition incomplete given the diffuse infiltrative nature of the tumour and the inability to remove it entirely without causing too much harm to the healthy brain. A major challenge in therapy of GB is the selection of the area for maximum safe resection of the tumour in order to reduce the degree and time to tumour recurrence while at the same time affecting the patient functionality as less as possible [6].

16.3.2 Post-surgery Decision

What is the molecular subtype of GB? What are the implications of GB subtyping in patient prognosis, treatment and follow-up? In recent years, analysis of genomics, transcriptomics and proteomics have identified subtypes of GB with prognostic implications and different responses to treatment. After surgery, it is possible to characterise the molecular subtype of GB using high-throughput arrays and immunohistochemistry techniques. Moreover, liquid biopsy may provide a wide set of biomarkers related to diagnosis, prognosis and treatment response. These biomarkers can circumvent problems of tumour heterogeneity and can be obtained to monitor tumour changes over time. It is now fully clear that different genetic subtypes of GB exist, associated with differences in molecular pathways involved and in biological behaviour. Therefore, clinical questions related to the prognosis and treatment response will be analysed in the context of knowledge of the molecular and genetic underpinnings.

16.3.3 Pre-radiotherapy Decision

What are the best RT dose value, distribution and technique for a specific patient? Currently the RT dose is estimated homogeneously based on anatomical images from PET or magnetic resonance (MR) scanners. The challenge in the use of RT is to reduce the margins beyond the conventional clinical target volume to the minimum in order to have optimised planning target volumes in accordance with the ICRU 62 definitions [7]. A reduction of RT treatment region uncertainty and a better estimation of the RT dose distribution based on the integration of functional information extracted from the images with dose painting could allow reduction of the radiation applied to brain functional areas where necessary and increase of radiation where possible, thereby improving the quality of life of the patients and their survival times.

16.3.4 Follow-Up Decisions

Is the treatment working properly? What should be the duration of adjuvant CHTH? What is the best treatment management during follow-up? Accurate interpretation of MRI scans in terms of

the biological evolution of the tumour is an important issue for measuring treatment response both in the setting of clinical trials and in routine clinical care. However, the evaluation of the disease progression still remains a difficult task in the face of treatment modality. Pseudoprogression of tumour versus true progression has become a confusing issue after treatment with TMZ and RT. Radiation injury (radionecrosis) is a potential late complication of RT, especially focal high-dose RT, and can easily be confused with tumour progression. Differentiating the two entities is problematic and often requires long-term follow-up with standard MRI, clinical assessment and use of corticosteroids [1]. By contrast, pseudo-responses may occur after angiogenesis-targeted therapies, as a consequence of changes in vascular permeability. In this sense, an early and accurate assessment of treatment response will improve the decision on maintenance or discontinuation of adjuvant CHTH, as well as the election and timing of subsequent treatments, including second-line CHTH and new local therapies.

16.4 Imaging Biomarkers in Glioblastoma Management

The development of imaging biomarkers is providing new insights into tumour behaviour that were not available from conventional medical imaging. Imaging biomarkers have demonstrated to be relevant for the assessment of tumour grading and response to therapy, without any spatial or temporal constraints. These imaging biomarkers are based on imaging modalities such as PWI, DWI, MRSI and PET.

The inclusion of PWI biomarkers characterising the presence and properties of angiogenesis, vasculogenesis and tumour vascular heterogeneity might improve tumour grading, prognosis and follow-up evaluation [8–10]. The complex modelling of dynamic susceptibility contrast (DSC) MRI sequences has also allowed for the quantification of tumour permeability and angiogenesis processes, through pharmacokinetic models of the lesion.

DWI may allow the cellularity of tumours to be graded noninvasively; because cells constitute a relative barrier to water diffusion, compared with extracerebral space, tumours that are more cellular are expected to show less of an increase in apparent diffusion coefficient (ADC) than tumours that are less cellular [15]. Diffusion tensor imaging and diffusion kurtosis imaging are used to describe diffusion 3D variability by means of mean diffusivity, fractional anisotropy and mean kurtosis. Several studies suggest that diffusion tensor imaging allows not only to observe high cellularity regions but also to evaluate tumour invasion into the surrounding tissue [16]. Studies of patients with brain tumours have shown that increases in water diffusion generally indicate positive response to therapy [15].

MRSI provides information regarding the concentration of specific metabolites throughout the brain, which has proven to be relevant in brain tumour diagnosis and prognosis. Thus, increased lipid levels are found in high-grade gliomas, indicating the presence of necrosis, which is a hallmark of GB [17]. Choline has been related to cell membrane density and is recognised as a marker of cell proliferation [17]. Statistically significant higher metabolite ratios of choline/creatine and choline/NAA have been reported in high-grade gliomas compared to low-grade gliomas [18]. Elevated choline levels have been found in peritumoural oedema surrounding GB, suggesting tumour invasion. After treatment, MRSI has also shown potential to differentiate tumour recurrence from radiation necrosis [19].

Several PET tracers have shown their added value when it comes to the diagnosis, prognosis and treatment monitoring of brain tumours. 18 F-FDG, which is a marker of glucose metabolism, has shown correlation with tumour grade and survival rate in gliomas [20]. Increased amino acid PET tracer uptake has been related to angiogenesis and increased cell metabolism within gliomas, resulting in a higher 11C-MET uptake in high-grade than in low-grade gliomas [21]. Labelled nucleotides such as 18 F-FLT are indicators of cellular proliferation, promoting 18 F-FLT kinetic analyses to assess early treatment response [22]. 18 F-FMISO is a hypoxia marker, showing increased uptake in high-grade

but not in low-grade gliomas. Tumour progression and survival after RT have been related to 18 F-FMISO uptake levels [23].

Hypoxia plays a central role in tumour development, angiogenesis, growth and resistance to treatment. Hypoxia measurements have been shown to correlate with the probability of metastatic spread, tumour recurrence, resistance to CHTH and radiation, invasion and decreased patient survival. Only a few imaging techniques have potential for in vivo assessment of hypoxia in humans, particularly for repeated, sequential measurements [24]. These methods use either PET tracers or MRI techniques sensitive to variations in local oxygen changes such as blood oxygenation level-dependent MRI (BOLD-MRI) or dynamic contrast-enhanced MRI (DCE-MRI)). An additional approach to map regional hypoxia is through the use of 3D MRSI and the quantification of lactate to N-acetyl-aspartate ratio with long echo times.

Although the added value of PWI, DWI, MRSI and PET is unmistakable, it has become clear that no single modality in itself is specific enough to show the early response to treatment of GB tumours due to their heterogeneity and evolution speed [4]. Hence, some groups have studied the complementary information provided by different modalities and techniques. Laimon et al. described the complementarity regarding tumour progression and response of dynamic [18 F] fluorothymidine (F-18 FLT) PET, sodium (23Na) MRI and 3-T morphological MRI biomarkers.

Manual segmentation is still the gold standard for brain tumours in clinical practice; however it implies a time-consuming and user-dependent bias, prone to errors and with questionable reproducibility. Significant progresses have been made in automated brain tumour segmentation based on machine learning [25–27]. Brain Tumour Segmentation (BRATS) Challenge on MICCAI Conference revealed that machine learning performs well in the whole tumour segmentation compared to manual segmentation. However, supervised learning requires an expensive, time-consuming and biased task to retrieve a sufficiently large set of labelled samples from which to learn discriminant functions for the posterior segmentation [26]. Moreover, spatio-temporal changes in clinical environment such as new MR machines, protocols or centres may distort the data and hence could affect the performance of the supervised models [28]. Unsupervised learning tackles these limitations in a more straightforward manner, as it directly learns the patient specific data to build an intra-patient segmentation model which is independent from the differences among patients [29].

16.5 New Trends for Integrated GB Management

Current clinical practices in GB management need to evolve to improve the poor results obtained to date in the treatment of this complex disease. To do so, the following promising approaches need to be particularly taken into account.

16.5.1 GB Molecular Subtypes

In the last decade, genomic analyses, transcriptomics and proteomics have identified different GB subtypes and molecular pathways with implications for prognosis and treatment response. For optimal management of patients, more precise classification of gliomas is needed, and molecular markers hold great promises in this respect.

The proneural subtype of GB, which is associated with better prognosis, is characterised by the expression of the histological markers OLIG2, DLL3, PDGFRA, IDH1 mutation (isocitrate dehydrogenase1), the absence of chromosomal gains or losses, the loss of TP53 heterozygosity and the normality of EGFR (epidermal growth factor receptor) as well as PTEN (phosphatase and tension homolog). The mesenchymal subtype, which corresponds to tumours of worse prognosis with strong angiogenic and inflammatory features, is characterised by the expression of mesenchymal markers such as YKL-40, PECAM1 (CD31), VEGF and its receptors one and two, gain of chromosome 7, loss of PTEN, normal or extended EGFR and MET, 17q11.2

deletion as well as high expression of genes of the TNF superfamily and NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) signalling pathway. Other less consensual subtypes are proliferative and classic, which share loss of PTEN and frequent EGFR amplification. Proliferative subtype is characterised by histological markers, such as TOP2A and PCNA (proliferative cell nuclear antigen), and loss of chromosome 10. The classic subtype harbours frequent amplification of chromosome 7, loss of chromosome 10, amplification of EGFR gene and absence of alterations in TP53, NF1, PDGFRA or IDH1 [3, 30, 31]. The neural subtype is characterised by neural markers. In retrospective studies, it was observed that classic and mesenchymal tumours benefited from combined treatment of RT plus TMZ, while in the proneural, TMZ did not seem to provide therapeutic benefits [3]. However, prospective studies are necessary to confirm these findings.

On the other hand, recent studies suggest that antiangiogenic therapy could be beneficial in the proneural subtype and possibly in the proliferative subtype, but not in the mesenchymal [32]. All in all, it is currently clear that GB constitutes a 'mixed bag' of tumours and that the diagnosis of particular molecular subtypes (especially those characterised by mutations in IDH1/IDH2, H3F3A, BRAF, EGFR variant III (EGFRvIII) or EGFR amplification) will be of relevance in daily clinical practice soon.

Given the complexity and costs of these studies, promising approaches endeavour to develop easy-to-use panels of workable tests in the clinical context able to provide a more precise classification of gliomas, such as the analysis of messenger RNA (mRNA) by Colman and coworkers [8], which identifies nine genes with prognostic value. Another study using immunohistochemistry methods used only three markers for the classification in proneural-like and classical-like subtypes (p53, PDGFRA and EGFR) [33]. In addition, the expression of specific proteins, such as OLIG2, DLL3, TOP2A, CD44, VEGF and FOXG1, has been validated as a feature of GB molecular subtypes. Notably, activation of the signalling pathways pErk1,2/pMAPK and pAKT has also shown its prognostic value in GB [9]. More recently, an innovative, minimal IHC-based scheme for GB subclass assignment was proposed in terms of positive staining for IDH1R132H for proneural, high-EGFR expression for the classical subtype and a combined high expression of PTEN, VIM and/or YKL40 for the mesenchymal subtype [10].

16.5.2 Key Enabling Molecular Biomarkers in the Clinical Practice

Tumour-derived molecular biomarkers include proteins, nucleic acids and tumour-derived extracellular vesicles. These molecular biomarkers are mainly identified in plasma, serum, blood platelets, urine and/or cerebrospinal fluid. These molecular biomarkers provide valuable information of the mechanisms associated with cancer hallmarks such as cell proliferation, tumour progression, invasion, cell cycle, angiogenesis and apoptosis. Recently, circulating tumour cells have also been identified in the blood of glioma patients. Circulating molecules, vesicles, 'tumour-educated' platelets and cells may be useful as easily accessible diagnostic, prognostic and/or predictive biomarkers to guide the patient management.

There is an increasing interest in identifying the protein profile of each GB subtype from peripheral blood samples, in addition to the immunohistochemical analysis of a small set of proteins for GB stratification and the activation of key signalling pathways to identify potential therapeutic targets. A different hypothesis suggests that the data obtained will allow the correlation of a simple immunohistological classification pattern with cell-free circulating proteins that may be used to predict prognosis as well as therapeutic response. If this hypothesis is confirmed, it is expected that a wide perspective will be opened for identifying new and more effective therapeutic targets. In this sense, advanced approaches aim to incorporate an accurate selection of molecular biomarkers (e.g. IHC, NGS, methylation status and chromosomal copy number aber-

rations) including those obtained from liquid biopsy in the clinical management of GB (e.g. cell-free circulating proteins and RNA sequencing of 'tumour-educated' blood platelets).

Thereby, these approaches may help to circumvent problems related to tumour heterogeneity and sampling error at the time of diagnosis. If the success of these methodologies is confirmed, it is expected that a wide perspective will be opened for identifying more informative biomarkers with diagnostic, prognostic, predictive and/or monitoring value and innovative, more promising therapeutic targets.

16.5.3 Advanced Multiscale Data Modelling in GB: In Silico Oncology Models

The main approaches for multiscale mathematical modelling of cancer have as a common starting point the fact that cancer is a genetic disease and that its evolution is related, since the very early stage to mutations that give acquired abilities in few or even single cells [34, 35]. The observation that the biological system under consideration has multiscale features has resulted in the development of mathematical models that essentially couple different models operating at different scales and that are able to cope with genomics, proteomics, cell-cell interaction, cell-environment interaction, release, diffusion and absorption of chemical factors. Specifically, the modelling of cancer dynamics at the lowest scale, namely, molecular and cellular scale, focuses on the critical changes within the cell that characterise cancer growth. These changes (i.e. self-sufficiency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, evading immune system attack and tissue invasion and metastasis) incorporate some aspects of genetic mutation, gene expression and evolutionary selection, leading to malignant progression. In various cases, this evolution is induced by external or concomitant actions (as an example, the effect of therapies) [36]. At the tissue scale, macroscopic models of gliomas focus on the heterogeneous and anisotropic characteristics of the brain-deducing models that are able to describe the growth of tumour masses and the diffusion of metastases in such an environment [37, 38].

There are two major cancer-modelling schools that may be identified: predominantly continuous and predominantly discrete models. Predominantly continuous models rely primarily on differential equations to describe processes such as diffusion of molecules, changes in tumour cell density and invasion of tumour cells into the surrounding tissue. Even the continuous mathematical models, which make use of partial ordinary differentiation equations and appropriate boundary conditions, have to undergo discretisation through the application of methods such as finite difference time domain or finite element techniques in order to practically deal with the high geometrical complexity of the biomechanical problem.

A tumour growth modelling approach based solely on the continuous and/or finitised form of the diffusion's reaction equation has a limited potential to efficiently address the complexities of the treatment response phenomena in the multiscale context. The latter include inter alia the existence and dynamics of different proliferation potential cell categories (stem cells, limited mitotic potential cells, differentiated cells), different cell-cycle phases (G1, S, G2, M), different radiosensitivity and chemosensitivity profiles, different times spent within each cell-cycle phase, etc.

Discrete modelling has gained significant momentum lately; it considers several discrete states in which cells may be found and possible transitions between them, governed by decision calculators, such as cytokinetic diagrams and agent-based techniques. Due to the hypercomplexity of cancer-related topics, each modelling approach is intrinsically able to successfully address only some of the aspects of this multifaceted problem. By combining the continuous and the discrete mathematical approaches, more comprehensive hybrid models addressing both glioma invasion and response to complex treatment modalities could emerge.

The ultimate goal of clinically oriented cancer simulation models is their eventual translation into clinical practice, which entails (a) thorough sensitivity analyses, in order to both comprehend and validate their behaviour, and at the same time gain further insight into the simulated mechanisms, in a more quantitative way, and (b) an adaptation and validation process based on real clinical data [39]. On the global level, the first large-scale, clinical trial-driven and clinically adaptable and testable oncosimulators have been developed by the In Silico Oncology and In Silico Medicine Group (ISO and ISMG) of the Institute of Communication and Computer Systems (ICCS), National Technical University of Athens (NTUA), in the context of the ACGT FP6 EU project (http://acgt.ercim.eu/) for nephroblastoma and breast cancer within the framework of the SIOP 2001/GPOH (http://www.siop-online.org/) and the neoadjuvant trial of principle (TOP) clinical trials, respectively.

16.6 Including Key Enabling Technologies in Clinical Practice

After reviewing the new trends in GB management, we are ready to present an approach to cover the gap between the technologies (i.e. existing molecular GB subtyping techniques, multiscale-multilevel predictive models and biomarker images) and their integration in the clinical workflow for the management of GB patients.

Our approach consists on the development of a clinical DSS to support multidisciplinary tumour boards in the therapy planning and early treatment response assessment of GB, that is, a health information technology system designed to assist the different actors involved in the GB management with main clinical decision-making tasks. The proposed DSS will use heterogeneous data to support and personalise treatment and follow-up for GB patients (see Fig. 16.2). The main functionalities to achieve this goal are:

1. Accessible and structured data: To be able to access the heterogeneous data in a transparent and secure way by developing interoperability and security layers.
2. Generation of knowledge: The novel image analysis tools will generate segmentations of the GB extension, hallmark and nosological images and hypoxia mappings. The findings obtained from imaging data together with molecular and clinical information will feed the multiscale-multilevel predictive models to obtain predictions of the evolution of the tumour depending on the simulated treatment. Finally an automatic characterisation of the GB molecular subtype will be done.
3. Support to clinical decision: Once the knowledge that addresses the clinical questions is generated, it will be used to support the clinical decisions. The DSS will adapt the presentation of their outputs to the clinical workflow. Two main scenarios have been considered: the first one is the scenario where the clinician wants to access the DSS findings using the hospital electronic health record (EHR) viewer. The DSS will include visualisation templates for EHR viewers tailored to each user profile. The second one is the tumour board multidisciplinary scenario. In this scenario, the DSS will facilitate a multidisciplinary collaborative interface including the latest visual and interactive technologies to improve user experience and acceptability.

A large body of evidence over many years suggests that DSS can be helpful in improving both clinical outcomes and adherence to evidence-based guidelines. However, to this day, clinical decision support systems are not widely used outside of a small number of sites, the main reasons being (1) the relative difficulty of integrating such systems into clinical workflows and computer systems, (2) the acceptability by the final users (user experience) and (3) the capability of keeping DSS up to date [40].

In the case of GB, the fulfilment of these requirements is even more challenging due to the wide variety of multidisciplinary users that will interact with the DSS; the need for acquiring, integrating and processing a wide variety of complex clinical information (ranging from molecu-

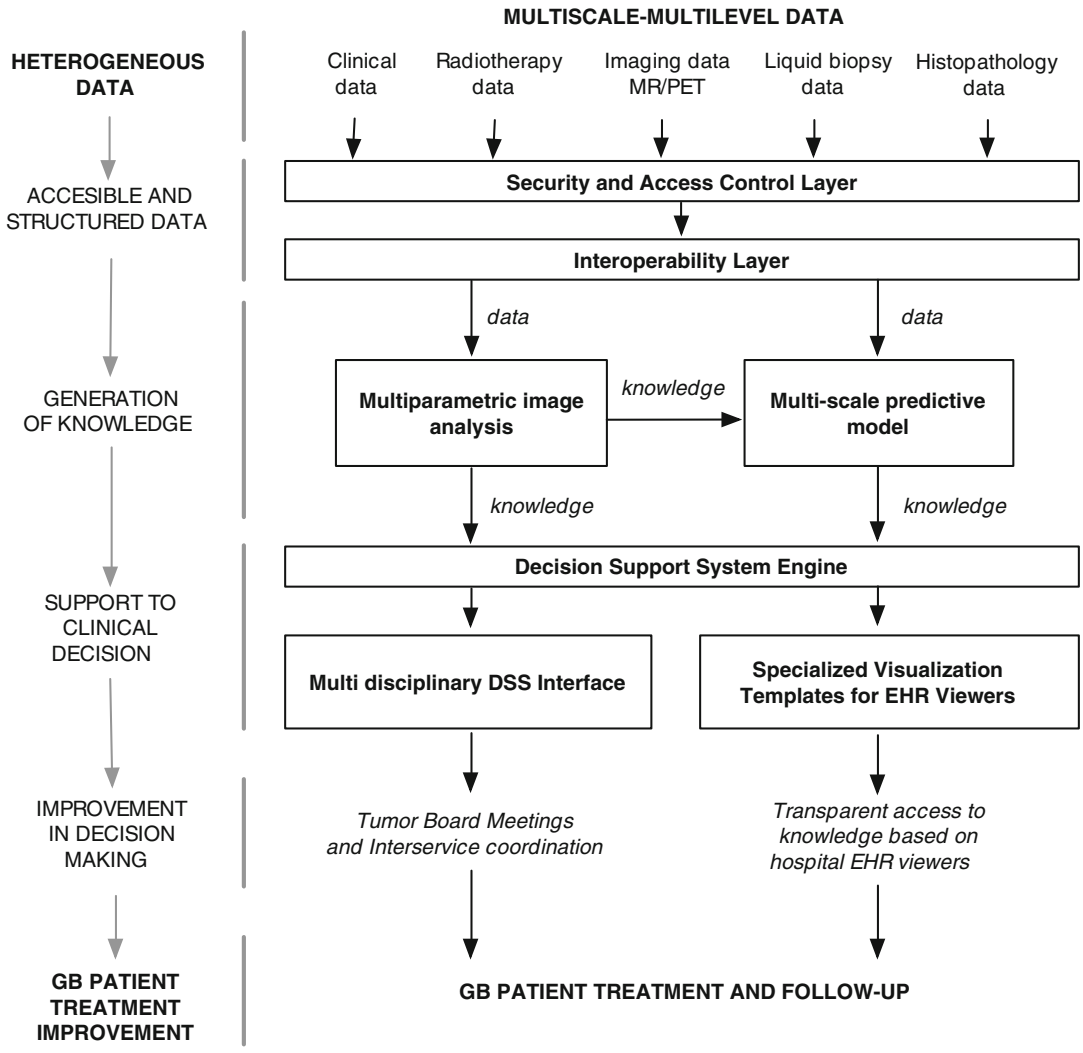

Fig. 16.2 Conceptual diagram of an advanced multiscale data modelling for GB management

lar data to multi-parametric stacks of images); and the need for covering the whole management of GB patients including surgery and RT planning and CHTH assessment.

A tentative schema of how the proposed DSS could be integrated in a clinical scenario is presented in Fig. 16.3. In this figure, we can see (1) how the DSS is integrated with the hospital clinical information systems, (2) how the results of the DSS are presented to the actors involved in the GB patient management by using specialised EHR-based visualisation templates and dedicated multidisciplinary DSS interface for tumour board meetings and (3) the structure of the DSS architecture.

In the following subsection, we will detail our approach to overcome the above section barriers:

16.6.1 Integrating the DSS into Clinical Workflows and Computer Systems

In order to facilitate the adoption of a DSS for GB management, it is critical to implement the mechanisms to accomplish the semantic interop-

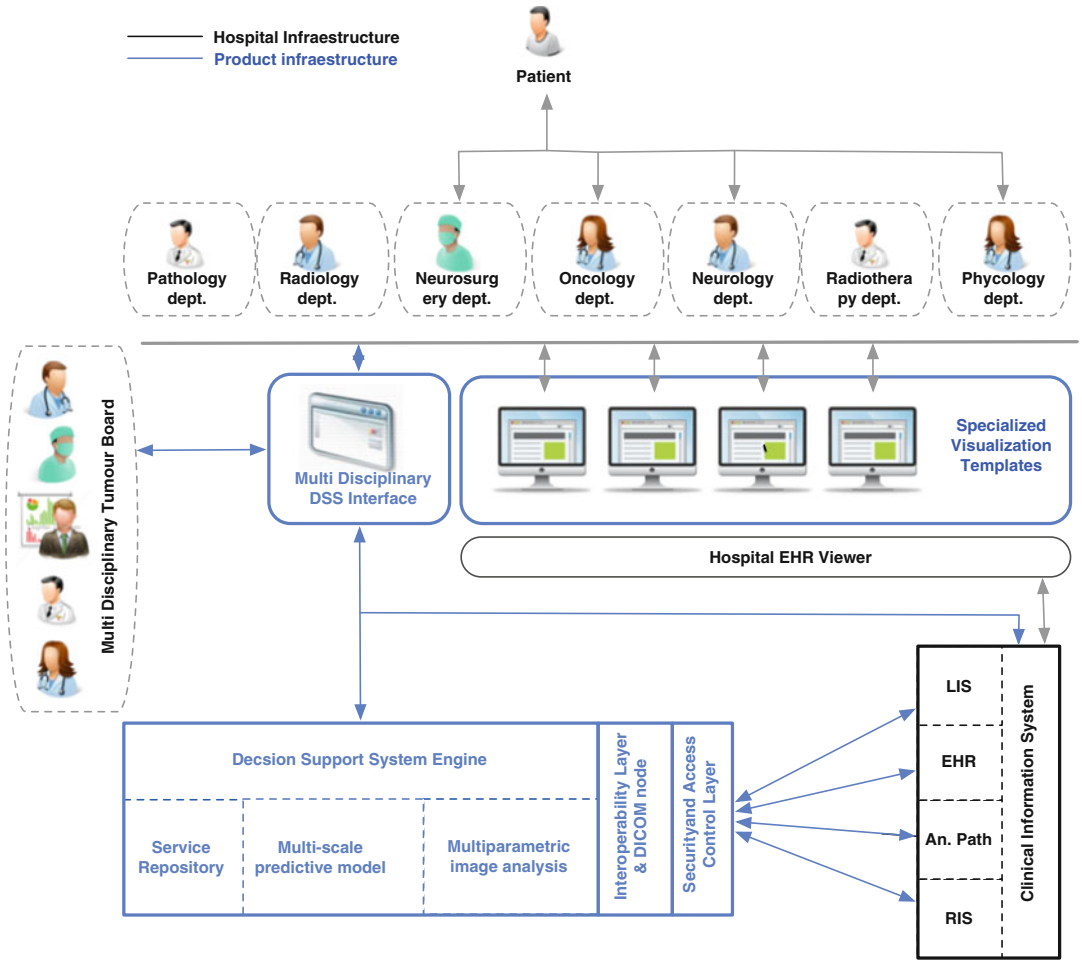

Fig. 16.3 Schema of an advanced DSS integrated in a clinical scenario. The DSS modules and connections are represented in *blue*, while the hospital infrastructures are represented in *black*

erability and complete integration with the existing hospital information systems. Following the interoperability standards and IHE profiles, we will ensure the integration and communication with different IT products already established in the IT infrastructure of the hospitals, enabling data capture from existing RIS/pathology/LIS/EHR systems. From our previous experience, this facilitates the adoption of the system at end-user level by presenting an already familiar user interface, reducing the requirements for manual data recording as well as the elimination of errors in the management of complex data by means of automation and integration at both hardware and software boundaries.

Moreover, it is important to make the DSS results accessible to clinicians at the moment when decisions are taken. To do this, we propose a double strategy consisting on the development of (1) highly visual user interfaces tailored for each of the multiple hospital areas involved in the tumour treatment and (2) an interactive interface and automatic reports for the multidisciplinary meetings.

As a result, the DSS will be fully integrated in the hospital workflows by means of the IHE profiles, which will ensure the sharing of the complete information, as well as the control and coordination of all the medical services involved in the GB management.

16.6.2 The Acceptability by the End Users

One of the major reasons why so many DSS are not used in clinical practice is that they lack positive user experience. Thus, the design of the graphical user interface (GUI) is of paramount importance in any healthcare tool and DSS development since it is the steering wheel. One could say that the GUI is actually as important as the accuracy of the algorithm and it should be intuitive and user-friendly and fulfil the needs of the user(s).

In the medical field, we are witnessing the situation that with more and more specialised examinations, tests and monitoring, physicians are faced with a significant amount of different but related pieces of information on each patient. Moreover, medical work is collaborative. Thus, for a patient with a brain tumour, several medical specialties and competences (i.e. neurologists, neurosurgeons, radiologists, oncologists, radiotherapists, (neuro)pathologists and clinical psychologists) must gather in several multidisciplinary team meetings (i.e. tumour board meetings), to present their findings and collaboratively discuss the diagnosis, treatment and follow-up. Although these tumour board meetings are part of the healthcare work process, there is room for improvement, particularly by tools that would facilitate the multidisciplinary meetings' flow and the access to multiscale information and would support the medical decision.

Identifying how technology can improve specialist interactions and enhance awareness at multidisciplinary meetings delivers real benefits [41]. In this chapter, we aim to design a GUI that will improve patient information visualisation and the interaction in tumour board meetings.

There have been a number of research studies for the improvement of displaying medical information when dealing with multiscale information. In [42], it is shown that using advanced visualisation techniques helps clinicians in improving their work process. Moreover, in [43], it is demonstrated that improved patient information visualisation is given by showing details prominently and presenting overviews.

Due to the extraordinary boost of technology in the field of human-machine devices, special attention was given in the last years to human-machine interaction and therefore to the user interface design. A number of diverse methodologies outlining techniques for human-computer interaction design have emerged in the last years. Among them UX methodology is the most popular as it is the best approach for evaluating how the user perceives the system before, during and after interacting with it. UX methodology is very intuitive and user-friendly and therefore highly recommended in clinics as several studies suggest that user involvement is crucial to a successful design and implementation of a successful tool for healthcare (see [44]). To avoid a top-down approach of designing a GUI for healthcare, close collaboration is needed between designers, implementers and the end users.

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